Population Genetics Concepts

Introduction

The Hardy-Weinberg equation sometimes predicts something about a population that doesn't come to be, because it works only when several criteria are met:

Population is **very large**

Allowance of **random mating**

The population must be **isolated** from other populations (no immigration or emigration)

Every individual has equal chance at survival—there's **no natural selection**

There are **no new mutations.**

While that's nice for a theoretical model in a scientific experiment, it doesn't always work out so well for human beings. Society, culture, geography, language, race, and more all influence what humans actually do. This lesson is going to explore some of the concepts that make the Hardy-Weinberg equation unreliable.

New Mutations

New mutations, those that are spontaneous and can alter expression of genes in a meaningful way, simply take too long for people to notice. A given practitioner of medicine will live fewer than one hundred years, and likely practice medicine for fewer than forty years. It takes tens of thousands of years for a spontaneous mutation to alter the path of a species. **Spontaneous** mutations are **slow** to occur. Since **most DNA is spacer DNA**, most mutations have no impact at all. This is how evolution occurs and new alleles arise, but it's effectively irrelevant for the provider of medicine.

Induced mutations by humans can speed up the rate at which mutations occur. This happens when a human touches uranium without a suit, or a radiologist unprotected by lead is exposed to forty years of radiation. Man-made mutations are **fast** and **always harmful** because the mechanism by which they are induced overwhelms the DNA repair mechanisms—they're not a new expression of a gene in response to the environment, but rather errors that lead to cell death or malignant transformation.

Recombination

If recombination occurs in a **gamete**, it effectively causes **no symptoms** in the organism made from that gamete because this generation has **no change in DNA complement**. All of the genes are present, though they may not be present in the same place or even on the same chromosome, as they ought to be. For the organism that grew out of the gamete that had this recombination, there's **no effect**—the complete genetic complement is present. But for the gametes this person produces, and therefore the offspring this person produces, there is **significantly increased risk** for genetic disease. (We explore this in lesson #7, *Chromosome Structure Diseases.*)

If instead there's a **somatic mutation** (one cell has a recombination during mitosis and is abnormal amongst billions of cells that don't have that recombination), all the good cells **should compensate** for that mutation. Their sheer number makes the somatic mutation in one cell irrelevant. This is true in all conditions save one: cancer. **Tumor suppressors** that get turned off (protein p53) or **oncogenes** that get turned on (BCR-ABL) as a result will cause malignancy. And even though it starts with one cell, that malignant cell escapes mechanisms that limit its growth, and cancer arises. We discuss both p53 and BCR-ABL in detail in the Inflammation and Cancer series.

Natural Selection

The individuals that survive and reproduce pass on genes. Those genes that allow the organism to survive and reproduce are more likely to be passed on. Certain alleles provide traits that create a better ability to survive. For this course, our working premise is that **p** is the **good allele** and **q** is the **bad allele**.

In **autosomal recessive** disorders, the bad allele is selected out because the organism dies before it can reproduce. This reduces the frequency of the bad allele. And, as we know, for some of the deadlier autosomal recessive disorders the frequency only becomes relevant in populations that are smaller and isolated (more on this later). **q should decrease** through natural selection.

But "p is good, q is bad" is not always the case. The **genes that increase survival persist**. A great example of this is sickle cell anemia, which has a substantially increased prevalence in Africans living in Africa and a much higher prevalence in African Americans than in the American Caucasian population. This is because the normal β-globin gene (p) doesn't improve survival—it isn't "good" by default. The bad β-globin gene (q) doesn't improve survival either. In fact, homozygous qq is a devastating disease that leaves patients with crippling pain their entire life and causes early death without medical intervention. But the carrier state pq provides a survival benefit over the homozygous normal. This all happens because the pq genotype **survives malaria better.** Malaria is endemic in much of Africa.

	p2	pp	HgbA2	Dies from malaria
Sickle Cell Anemia	2pq	pq	HgbSC	Survives malaria Survives anemia
	q2	qq	HgbSS	Dies from sickle cell

Table 5.1: Various Possibilities of Sickle Cell Genetics
Homozygous dominant wild type should live, but they die of malaria. Homozygous recessive results in the crippling disease sickle cell anemia, and the children die of sickle cell. But heterozygous individuals have the survival benefit of hemoglobin poor enough to resist malaria and good enough to not have sickle cell disease.

Malaria is an environmental pressure that forced the frequency of the carrier state to be favored over the normal state. Even though the diseased state is catastrophic—selecting out genotypes with both diseased alleles—the carrier state survived, as malaria selected out individuals with both normal hemoglobin alleles.

Here in the U.S., with medical therapies the homozygous recessive genotype isn't fatal. Medicines have prolonged and improved the quality of life of those affected. It's still quite a brutal disease and predominantly affects African Americans. But consider what this does genetically—by treating a treatable disease, we increase the diseased allele frequency by preventing natural selection, allowing individuals who normally would have died out to live, grow, and procreate.

Sickle cell demonstrates two points of natural selection. One, environmental factors influence which genes predominate. Those that offer a survival benefit tend to win over those that don't. Two, by treating patients with medications (practicing medicine), we can effectively increase the diseased allele.

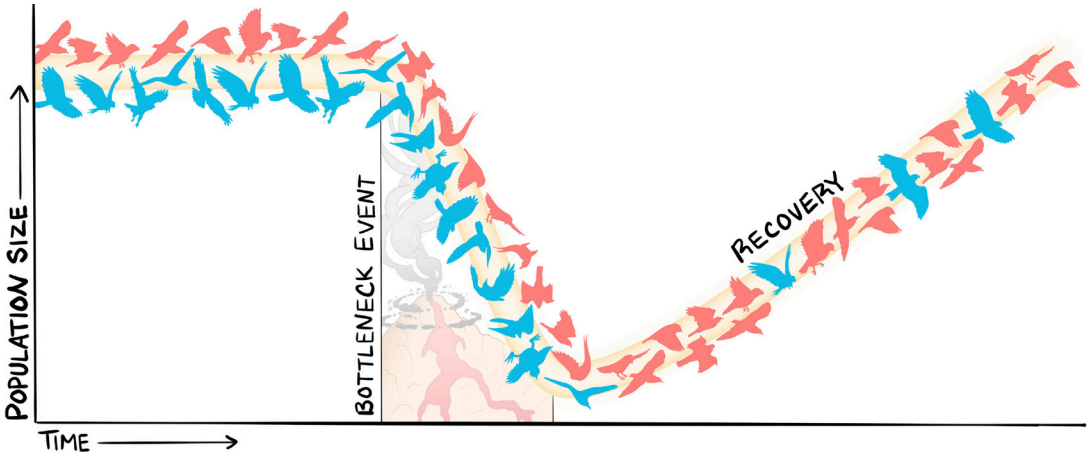
Genetic Drift

Genetic drift is what happens to allele frequency when **populations are too small**. The lesson on autosomal recessive diseases showed that the recurrence risk of two carriers is 25%. Every child they have has a 25% chance of being affected (disease). And yet some families have two children, both with the

affected state. Statistically speaking, when the N value is small, there's insufficient population to achieve statistical significance. This is a way of saying that **small populations don't adhere to math**. And it's true—to achieve the steady-state equilibrium of the Hardy-Weinberg equation, there must be a large population.

The **bottleneck effect** occurs when there's a drastic reduction in population size. The surviving individuals may not be a reflection of the larger parent population. This isn't natural selection—there wasn't a selection of one genotype for another, just random chance of a small population happened to end up this way. The surviving individuals then mate, and even though the population returns to normal numbers, the uneven distribution of genes of the original survivors alters the frequency with which they are encountered in the subsequent population.

The **founder effect** occurs when individuals are forced out of their natural gene pool and establish a gene pool of their own. For example, an ostracized population leaves its mother country to settle in the New World. The town that is founded has a small gene pool, and likely similar genes given the population's ostracized status.



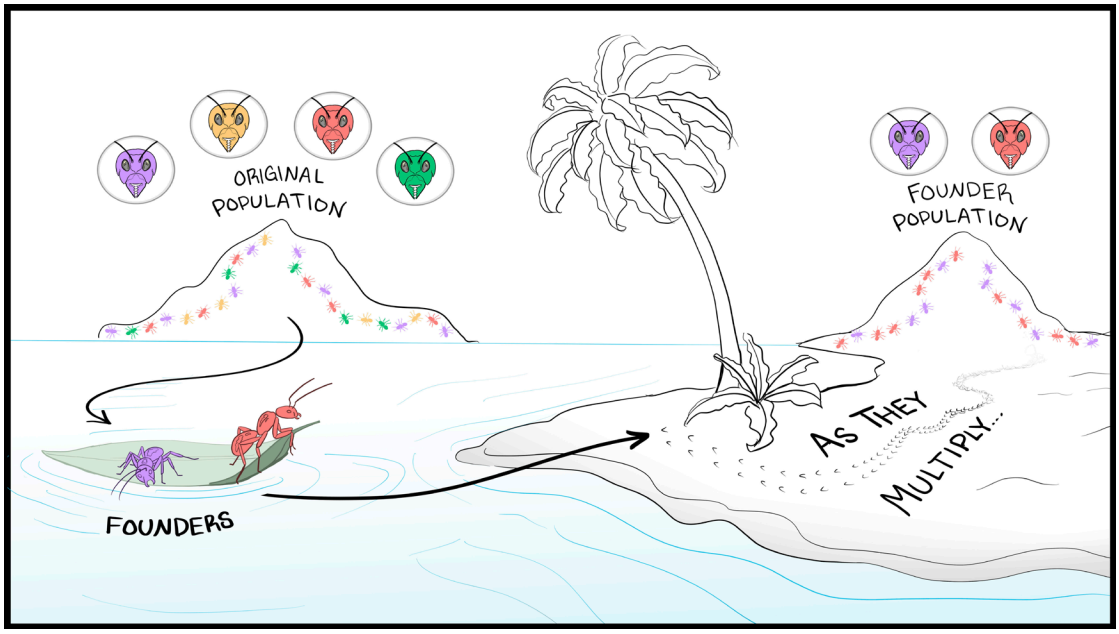


Figure 5.1, 5.2: Genetic Drift / Bottleneck / Founder Effect
In small populations, random chance wins out over statistical significance.

Gene Flow

What happens when **large populations mix**? Inherently, when more normal alleles are added to a population in a large way, the frequency of the diseased allele goes down. Just **by process of dilution**, already the frequency is less.

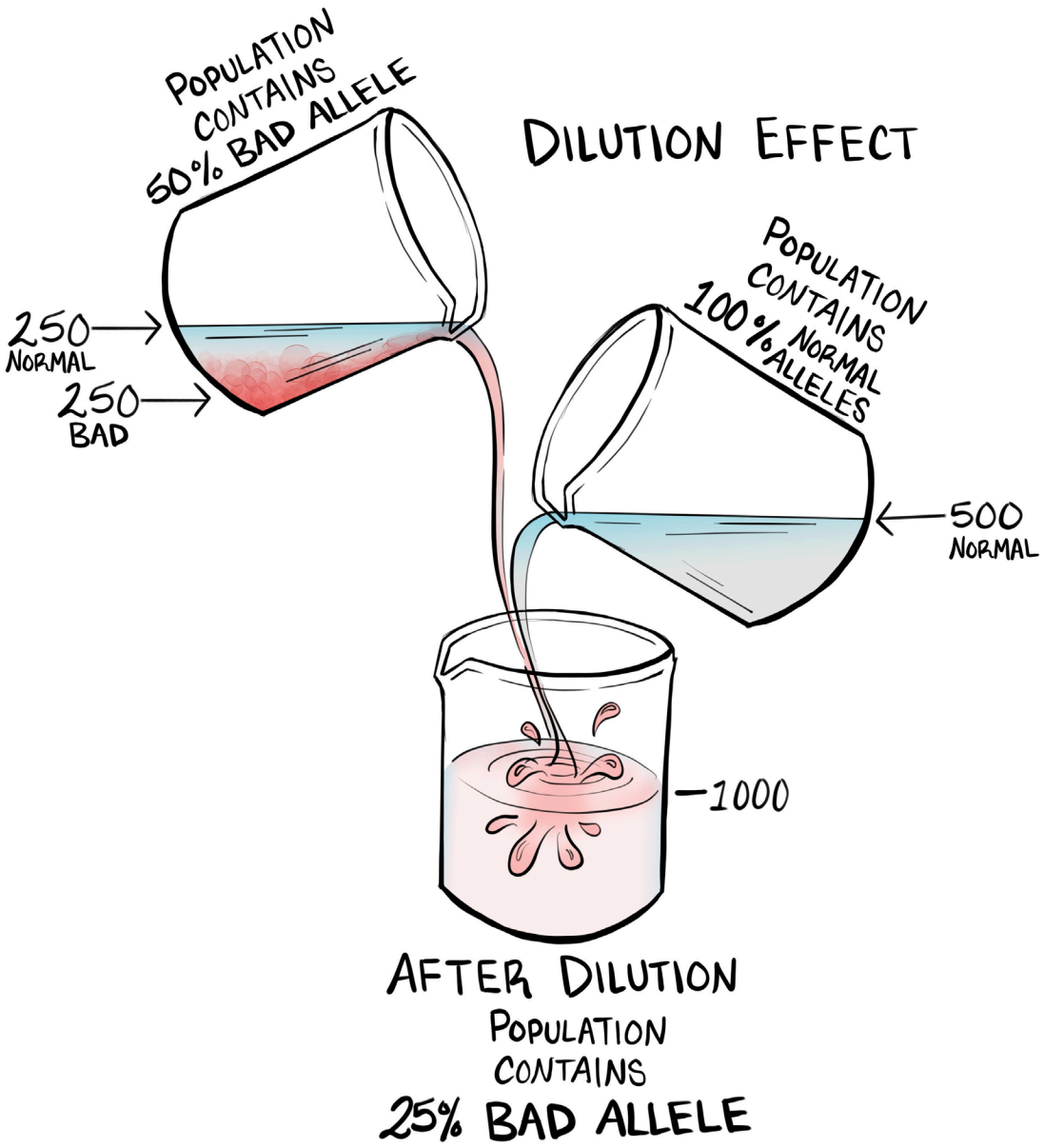


Figure 5.3: Gene Flow Dilution Effect
Mixing dissimilar gene pools dilutes out bad alleles.

And then the populations start interbreeding, allowing the alleles to mix, and the diseased allele gets reduced some more. It's simply that **populations that were separate and therefore different tend towards the average of the two populations**. Populations become less dissimilar with migration.

Consanguinity

Human populations sometimes interbreed, and **small populations mate internally**. This now has a stigma associated with it, as if it automatically assumes purposeful incest or sexual abuse. However, consanguinity most likely had to do with the local pressures of human civilization. Whether a population was isolated geographically (Welsh), culturally (Ashkenazi Jews), or financially (royal blood only mixed with royal blood), the selection of a smaller genetic pool **increases the risk of diseased alleles**. In order to increase the risk of a diseased allele in a small gene pool, a diseased allele must already be present. If the genes of all individuals in a consanguineous family were flawless with no mutations occurring, then pairing of similar DNA wouldn't matter. But no DNA is perfect, so when similar genetic material is intermixed, the diseased allele increases in frequency. Because often autosomal recessive disorders are fatal or sterilizing, the **carrier states for diseased alleles increase significantly.**

The concept of **coefficient of consanguinity** isn't tested much, but is useful when counseling patients. From the **perspective of the child**, there's a **50%** similarity between the child and its **mother**, **father**, and **siblings**. With one degree of separation there's ½ distancing. The **uncle/aunt** and the **child** have **two degrees of separation** and share **25%** (or ¼) of the DNA. The **cousin** and the **child** have three degrees of separation (child → parents → uncle → uncle's child) and share 1/8 of the DNA. Significant separation happens quite quickly. Second cousins can legally marry in the United States but are recommended not to.

Ashkenazi Jews see a **high incidence of Tay-Sachs** disease, which is nearly absent from other populations. The inbreeding of **Russian royalty** resulted in **hemophilia**.